AMENDMENT

In the Claims:

Please amend claims 1-5 as indicated below (for the convenience of the Examiner, all claims pending following entry of this amendment are presented below):

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1. (Amended) A method of downmodulating the immune response to an intestinal allograft in a subject comprising administering a therapeutic composition to the subject wherein the therapeutic composition consists of an antibody that binds to B7-1 and an antibody that binds to B7-2, such that the immune response to an intestinal allograft in a subject is downmodulated by the therapeutic composition.

2. (Amended) The method of claim 1, wherein a second therapeutic composition consisting of a rapamycin compound is administered to the subject.

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3. (Amended) A method of downmodulating the immune response to an intestinal allograft in a subject comprising pretreating said subject prior to said intestinal allograft with a therapeutic composition consisting of an antibody that binds B7-1, an antibody that binds B7-2 and a rapamycin compound, such that the immune response to an intestinal allograft in a subject is downmodulated by the therapeutic composition.

4. (Amended) A method of downmodulating the immune response to an intestinal allograft in a subject comprising post-treating said subject after said intestinal allograft with a therapeutic composition consisting of an antibody that binds B7-1, an antibody that binds B7-2, and a rapamycin compound, such that the immune response to an intestinal allograft in a subject is downmodulated by the therapeutic composition.

5. (Amended) A method of downmodulating the immune response to an intestinal allograft in a subject comprising pretreating said subject prior to said intestinal allograft and post-treating said subject after said intestinal allograft with a therapeutic composition consisting of an antibody that binds B7-1, an antibody that binds B7-2, and a rapamycin compound, such that the immune response to an intestinal allograft in a subject is downmodulated by the therapeutic composition.

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In the Specification:

Please amend page 1, the paragraph under the heading "Related Applications," to read:

A2

The present application claims priority to U.S. Provisional Patent Application Serial No. 60/189,165, filed March 14, 2000, entitled "Use of a Combination of Anti-B7-1 and Anti-B7-2 Antibodies in Inhibiting Intestinal Allo Graft Rejection", the entire contents of which are expressly incorporated herein by reference.

Please amend page 1, the last paragraph, to read:

A3

The CD80 (B7-1) and CD86 (B7-2) proteins, expressed on APCs, are critical costimulatory molecules (Freeman et al. 1991. *J. Exp. Med.* 174:625; Freeman et al. 1989 *J. Immunol.* 143:2714; Azuma et al. 1993 *Nature* 366:76; Freeman et al. 1993. *Science* 262:909). B7-2 appears to play a predominant role during primary immune responses, while B7-1, which is upregulated later in the course of an immune response, may be important in prolonging primary T cell responses or costimulating secondary T cell responses (Bluestone. 1995. *Immunity.* 2:555).

Please amend page 2, the first paragraph, to read:

A4

One receptor to which B7-1 and B7-2 bind, CD28, is constitutively expressed on resting T cells and increases in expression after activation. After signaling through the T

cell receptor, ligation of CD28 and transduction of a costimulatory signal induces T cells to proliferate and secrete IL-2 (Linsley, P.S., et al. 1991 *J. Exp. Med.* 173, 721-730; Gimmi, C.D., et al. 1991 *Proc. Natl. Acad. Sci. USA.* 88, 6575-6579; June, C.H., et al. 1990 *Immunol. Today.* 11, 211-6; Harding, F.A., et al. 1992 *Nature.* 356, 607-609). A second receptor, termed CTLA4 (CD152) is homologous to CD28 but is not expressed on resting T cells and appears following T cell activation (Brunet, J.F., et al., 1987 *Nature* 328, 267-270). CTLA4 appears to be critical in negative regulation of T cell responses (Waterhouse et al. 1995. *Science* 270:985). Blockade of CTLA4 has been found to remove inhibitory signals, while aggregation of CTLA4 has been found to provide inhibitory signals that downregulate T cell responses (Allison and Krummel. 1995. *Science* 270:932). The B7 molecules have a higher affinity for CTLA4 than for CD28 (Linsley, P.S., et al., 1991 *J. Exp. Med.* 174, 561-569) and B7-1 and B7-2 have been found to bind to distinct regions of the CTLA4 molecule and have different kinetics of binding to CTLA4 (Linsley et al. 1994. *Immunity.* 1:793).

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Please amend page 2, the last paragraph, to read:

The importance of the B7:CD28/CTLA4 costimulatory pathway has been demonstrated *in vitro* and in several *in vivo* model systems. Blockade of this costimulatory pathway results in the development of antigen specific tolerance in murine and humans systems (Harding, F.A., et al. (1992) *Nature.* 356, 607-609; Lenschow, D.J., et al. (1992) *Science.* 257, 789-792; Turka, L.A., et al. (1992) *Proc. Natl. Acad. Sci. USA.* 89, 11102-11105; Gimmi, C.D., et al. (1993) *Proc. Natl. Acad. Sci USA* 90, 6586-6590; Boussiotis, V., et al. (1993) *J. Exp. Med.* 178, 1753-1763). Conversely, expression of B7-1 by B7-1 negative murine tumor cells induces T-cell mediated specific immunity accompanied by tumor

A5

Please amend page 3, paragraphs 4-6, to read:

In another embodiment, the invention provides a method of downmodulating the immune response to an intestinal allograft in a subject comprising pretreating the subject

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prior to the intestinal allograft with an antibody that binds to B7-1, an antibody that binds to B7-2, and a rapamycin compound.

In another embodiment, the invention provides a method of downmodulating the immune response to an intestinal allograft in a subject comprising post-treating the subject after the intestinal allograft with an antibody that binds to subject with an antibody that binds to B7-1, an antibody that binds to B7-2 and a rapamycin compound.

In another embodiment, the invention provides a method of downmodulating the immune response to an intestinal allograft in a subject comprising pretreating the subject before the intestinal allograft and post-treating the subject after the intestinal allograft with an antibody that binds to B7-1, an antibody that binds to B7-2, and a rapamycin compound.

Please amend page 4, the fourth paragraph, to read:

As used herein, the term "costimulate" with reference to activated immune cells includes the ability of a costimulatory molecule to provide a second, non- activating receptor mediated signal (a "costimulatory signal") that induces proliferation or effector function. For example, a costimulatory signal can result in cytokine secretion, e.g., in a T cell that has received a T cell-receptor-mediated signal. As used herein the term "costimulatory molecule" includes molecules which are present on antigen presenting cells (e.g., B7-1, B7-2, B7RP-1 (Yoshinaga et al. 1999. Nature 402:827), B7h (Swallow et al. 1999. Immunity. 11:423) and/or related molecules (e.g., homologs)) that bind to costimulatory receptors (e.g., CD28, CTLA4, ICOS (Hutloff et al. 1999. Nature 397:263), B7h ligand (Swallow et al. 1999. Immunity. 11:423) and/or related molecules) on T cells. These molecules are also collectively referred to herein as "B7 molecules."

Please amend page 7, the last paragraph, to read:

As used herein, the term "extracellular domain of a B7 molecule" includes a portion of a B7 molecule which, in the cell-associated form of a B7 molecule, is extracellular. A B7 extracellular domain includes the portion of a B7 molecule which

mediates binding to a costimulatory receptor, e.g., CD28, ICOS, and/or CTLA4. For example, the human B7-1 extracellular domain comprises from about amino acid 1 to about amino acid 208 and the human B7-2 extracellular domain comprises from about amino acid 24 to about amino acid 245. See, for example, B7-2 (Freeman et al. 1993 *Science*. 262:909; GenBank Accession numbers P42081 or A48754; or United States Patent 5,942,607); B7-1 (Freeman et al. *J. Exp. Med.* 1991. 174:625; GenBank Accession numbers P33681 or A45803; or United States Patent 5,858,776).

Please delete the third and fourth paragraphs on page 10.

Please amend page 11, the first paragraph, to read:

non-costimulatory molecule genes, (e.g., under conditions equivalent to 65°C in 5 X SSC (1 X SSC = 150 mM NaCl/ 0.15 M Na citrate)) can be used to make anti-B7 antibodies. Alternatively, DNA sequences which retain sequence identity over regions of the nucleic acid molecule which encode protein domains which are important in costimulatory molecule function, e.g., binding to other costimulatory molecules, can be used to produce costimulatory proteins which can be used as immunogens. Preferably, nonnaturally occurring costimulatory molecules have significant (e.g., greater than 70%, preferably greater than 80%, and more preferably greater than 90-95%) amino acid identity with a naturally occurring amino acid sequence of a costimulatory molecule extracellular domain.

Please amend page 12, the first paragraph, to read:

Using B7 cDNA molecules, peptides having an activity of B7 can be produced using standard techniques. Host cells transfected to express peptides can be any prokaryotic or eukaryotic cell. For example, a peptide having B7 activity can be expressed in bacterial cells such as *E. coli,* insect cells (baculovirus), yeast, or mammalian cells such as Chinese Hamster ovary cells (CHO) and NS0 cells. Other suitable host cells and expression vectors may be found in Goeddel, (1990) *supra* or are

known to those skilled in the art. Examples of vectors for expression in yeast *S. cerevisiae* include pYepSec1 (Baldari. et al., (1987) *Embo J.* 6:229-234), pMFa (Kurjan and Herskowitz, (1982) *Cell* 30:933-943), pJRY88 (Schultz et al., (1987) *Gene* 54:113-123), and pYES2 (Invitrogen Corporation, San Diego, CA). Baculovirus vectors available for expression of proteins in cultured insect cells (SF 9 cells) include the pAc series (Smith et al., (1983) *Mol. Cell Biol.* 3:2156-2165) and the pVL series (Lucklow, V.A., and Summers, M.D., (1989) *Virology* 170:31-39). Generally, COS cells (Gluzman, Y., (1981) *Cell* 23:175-182) are used in conjunction with such vectors as pCDM8 (Seed, B., (1987) *Nature* 329:840) for transient amplification/expression in mammalian cells, while CHO (dhfr$^-$ Chinese Hamster Ovary) cells are used with vectors such as pMT2PC (Kaufman et al. (1987), *EMBO J.* 6:187-195) for stable amplification/expression in mammalian cells. A preferred cell line for production of recombinant protein is the NS0 myeloma cell line available from the ECACC (catalog #85110503) and described in Galfre, G. and Milstein, C. ((1981) *Methods in Enzymology* 73(13):3-46; and *Preparation of Monoclonal Antibodies: Strategies and Procedures*, Academic Press, N.Y., N.Y). Vector DNA can be introduced into mammalian cells via conventional techniques such as calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, LIPOFECTIN™, or electroporation. Suitable methods for transforming host cells can be found in Sambrook et al. (*Molecular Cloning: A Laboratory Manual*, 2nd Edition, Cold Spring Harbor Laboratory press (1989)), and other laboratory textbooks. When used in mammalian cells, the expression vector's control functions are often provided by viral material. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and most frequently, Simian Virus 40.

A 10

Please amend page 13, the last paragraph, to read:

In one embodiment, variants of a B7 polypeptide which function as either B7 antagonists can be identified by screening combinatorial libraries of mutants, *e.g.*, truncation mutants, of a B7 (or B7 ligand) polypeptide for B7 antagonist activity. In one embodiment, a variegated library of B7 variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A

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variegated library of B7 variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into

[Please amend page 14, the first paragraph, to read:]

gene sequences such that a degenerate set of potential B7 or B7 ligand sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display) containing the set of B7 or B7 ligand sequences therein. There are a variety of methods which can be used to produce libraries of potential B7 or B7 ligand variants from a degenerate oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an appropriate expression vector. Use of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential B7 or B7 ligand sequences. Methods for synthesizing degenerate oligonucleotides are known in the art (see, *e.g.*, Narang, S. A. (1983) *Tetrahedron* 39:3; Itakura *et al.* (1984) *Annu. Rev. Biochem.* 53:323; Itakura *et al.* (1984) *Science* 198:1056; Ike *et al.* (1983) *Nucleic Acid Res.* 11:477).

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Please amend page 15, the second and third paragraphs, to read:

In one embodiment, cell based assays can be exploited to analyze a variegated B7 or B7 ligand library. For example, a library of expression vectors can be transfected into a cell line which ordinarily synthesizes B7 or B7 ligand. The transfected cells are then cultured such that B7 or B7 ligand and a particular mutant B7 or B7 ligand are secreted and the effect of expression of the mutant on B7 or B7 ligand activity can be detected, *e.g.*, by any of a number of functional assays. DNA can then be recovered from the cells which score for inhibition of B7 or B7 ligand activity, and the individual clones further characterized.

A12

In addition to B7 or B7 ligand polypeptides consisting only of naturally-occurring amino acids, B7 or B7 ligand peptidomimetics are also provided. Peptide analogs are commonly used in the pharmaceutical industry as non-peptide drugs with properties

analogous to those of the template peptide. These types of non-peptide compounds are termed "peptide mimetics" or "peptidomimetics" (Fauchere, J. (1986) *Adv. Drug Res.* 15:29; Veber and Freidinger (1985) TINS p.392; and Evans *et al.* (1987) *J. Med. Chem.* 30:1229, which are incorporated herein by reference) and are usually developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to therapeutically useful peptides can be used to produce an equivalent therapeutic or prophylactic effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (*i.e.*, a polypeptide that has a biological or pharmacological activity), such as human B7 or B7 ligand, but have one or more peptide linkages optionally replaced by a linkage selected from the group consisting of: -CH2NH-, -CH2S-, -CH2-CH2-, -CH=CH- (cis and trans), -COCH2-, -CH(OH)CH2-, and -CH2SO-, by methods known in the art and further described in the following references: Spatola, A. F. in "*Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins*" Weinstein, B., ed., Marcel Dekker, New York, p. 267 (1983); Spatola, A. F., Vega Data (March 1983), Vol. 1, Issue 3, "Peptide Backbone Modifications" (general review); Morley, J. S. (1980) *Trends Pharm. Sci.* pp. 463-468 (general review); Hudson, D. *et al.* (1979) *Int. J. Pept. Prot. Res.* 14:177-185 (-CH2NH-, CH2CH2-); Spatola, A. F. *et al.* (1986) *Life Sci.* 38:1243-1249 (-CH2-S); Hann, M. M. (1982) *J. Chem. Soc. Perkin Trans. I.* 307-314 (-CH-CH-, cis and trans); Almquist, R. G. *et al.* (190) *J. Med. Chem.* 23:1392-1398 (-COCH2-); Jennings-White, C. *et al.* (1982) *Tetrahedron Lett.* 23:2533 (-COCH2-); Szelke, M. *et al.* European Appln. EP 45665 (1982) CA: 97:39405 (1982)(-CH(OH)CH2-);

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Please amend page 16, the first and second paragraphs, to read:

A12

Holladay, M. W. *et al.* (1983) *Tetrahedron Lett.* (1983) 24:4401-4404 (-C(OH)CH2-); and Hruby, V. J. (1982) *Life Sci.* (1982) 31:189-199 (-CH2-S-); each of which is incorporated herein by reference. A particularly preferred non-peptide linkage is -CH2NH-. Such peptide mimetics may have significant advantages over polypeptide embodiments, including, for example: more economical production, greater chemical stability, enhanced pharmacological properties (half-life, absorption, potency, efficacy, etc.), altered specificity (*e.g.*, a broad-spectrum of biological activities), reduced

antigenicity, and others. Labeling of peptidomimetics usually involves covalent attachment of one or more labels, directly or through a spacer (*e.g.*, an amide group), to non-interfering position(s) on the peptidomimetic that are predicted by quantitative structure-activity data and/or molecular modeling. Such non-interfering positions generally are positions that do not form direct contacts with the macromolecule(s) to which the peptidomimetic binds, to produce the therapeutic effect. Derivitization (*e.g.*, labeling) of peptidomimetics should not substantially interfere with the desired biological or pharmacological activity of the peptidomimetic.

Systematic substitution of one or more amino acids of a B7 or B7 ligand amino acid sequence with a D-amino acid of the same type (*e.g.*, D-lysine in place of L-lysine) can be used to generate more stable peptides. In addition, constrained peptides comprising a B7 or B7 ligand amino acid sequence or a substantially identical sequence variation can be generated by methods known in the art (Rizo and Gierasch (1992) *Annu. Rev. Biochem.* 61:387, incorporated herein by reference); for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

A 12

The amino acid sequences of B7 or B7 ligand polypeptides identified herein will enable those of skill in the art to produce polypeptides corresponding to B7 or B7 ligand peptide sequences and sequence variants thereof. Such polypeptides can be produced in prokaryotic or eukaryotic host cells by expression of polynucleotides encoding a B7 or B7 ligand peptide sequence, frequently as part of a larger polypeptide. Alternatively, such peptides can be synthesized by chemical methods. Methods for expression of heterologous proteins in recombinant hosts, chemical synthesis of polypeptides, and *in vitro* translation are well known in the art and are described further in Maniatis *et al.* *Molecular Cloning: A Laboratory Manual* (1989), 2nd Ed., Cold Spring Harbor, N.Y.; Berger and Kimmel, Methods in Enzymology, Volume 152, Guide to Molecular Cloning Techniques (1987), Academic Press, Inc., San Diego, Calif.; Merrifield, J. (1969) *J. Am. Chem. Soc.* 91:501; Chaiken I. M. (1981) *CRC Crit. Rev. Biochem.* 11: 255; Kaiser *et al.* (1989) *Science*

Please amend page 17, the first paragraph, to read:

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243:187; Merrifield, B. (1986) *Science* 232:342; Kent, S. B. H. (1988) *Annu. Rev. Biochem.* 57:957; and Offord, R. E. (1980) *Semisynthetic Proteins*, Wiley Publishing, which are incorporated herein by reference.

Please amend page 18, the first paragraph, to read:

A13

Moreover, it will be appreciated by those skilled in the art that it is within their skill to generate additional agents and screen for their activity by following standard techniques. For instance, B7 molecules from a variety of species, whether in soluble form or membrane bound, can be used to induce the formation of anti-B7 antibodies. Such antibodies may either be polyclonal or monoclonal, or antigen binding fragments of such antibodies. Of particular significance for use in therapeutic applications are antibodies that inhibit binding of a B7 molecule with its natural ligand(s) on the surface of immune cells, thereby inhibiting costimulation of the immune cell through the B7-ligand interaction. Preferred anti-B7 antibodies are those capable of inhibiting or downregulating T cell mediated immune responses by binding the B7 molecule on the surface of B lymphocytes and preventing interaction of the B7 molecule with CTLA4 and/or CD28. Preferably, the combination of antibodies chosen for use in the invention results in increased inhibition of costimulation of an immune cell, such as a T cell, through the B7-ligand interaction, relative to either antibody alone.

Please amend page 21, the third paragraph, to read:

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Such mammal-produced populations of antibody molecules are referred to as "polyclonal" because the population comprises antibodies with differing immunospecificities and affinities for a costimulatory molecule. The antibody molecules are then collected from the mammal and isolated by well known techniques such as, for example, by using DEAE SEPHADEX™ to obtain the IgG fraction. To enhance the specificity of the antibody, the antibodies may be purified by immunoaffinity

chromatography using solid phase-affixed immunogen. The antibody is contacted with the solid phase-affixed immunogen for a period of time sufficient for the immunogen to immunoreact with the antibody molecules to form a solid phase-affixed immunocomplex. The bound antibodies are separated from the complex by standard techniques.

A 14

Please amend page 23, the first paragraph, to read:

(b) A suspension of antibody-producing cells removed from each immunized mammal secreting the desired antibody is then prepared. After a sufficient time, the mouse is sacrificed and somatic antibody-producing lymphocytes are obtained. Antibody-producing cells may be derived from the lymph nodes, spleens and peripheral blood of primed animals. Spleen cells are preferred, and can be mechanically separated into individual cells in a physiologically tolerable medium using methods well known in the art. Mouse lymphocytes give a higher percentage of stable fusions with the mouse myelomas described below. Rat, rabbit and frog somatic cells can also be used. The spleen cell chromosomes encoding desired immunoglobulins are immortalized by fusing the spleen cells with myeloma cells, generally in the presence of a fusing agent such as polyethylene glycol (PEG). Any of a number of myeloma cell lines may be used as a fusion partner according to standard techniques; for example, the P3-NS1/1-Ag4-1, P3-x63-Ag8.653 or Sp2/O-Ag14 myeloma lines. These myeloma lines are available from the American Type Culture Collection (ATCC™), 10801 University Boulevard, Manassas, VA 20110-2209.

A 15

Please amend page 31, the first paragraph, to read:

chains of the antibody such that the light and heavy chains are expressed in the host cell and, preferably, secreted into the medium in which the host cells are cultured, from which medium the antibodies can be recovered. Standard recombinant DNA methodologies are used to obtain antibody heavy and light chain genes, incorporate these genes into recombinant expression vectors and introduce the vectors into host cells, such as those described in Sambrook, Fritsch and Maniatis (eds), *Molecular Cloning; A Laboratory*

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Manual, Second Edition, Cold Spring Harbor, N.Y., (1989), Ausubel, F.M. *et al.* (eds.) *Current Protocols in Molecular Biology*, Greene Publishing Associates, (1989) and in U.S. Patent No. 4,816,397 by Boss *et al.*

Please amend page 31, the last paragraph, to read:

A17

To express the antibodies, or antigen binding portions of the invention, DNAs encoding partial or full-length light and heavy chains, obtained as described above, can be inserted into expression vectors such that the genes are operatively linked to transcriptional and translational control sequences. In this context, the term "operatively linked" is intended to mean that an antibody gene is ligated into a vector such that transcriptional and translational control sequences within the vector serve their intended function of regulating the transcription and translation of the antibody gene. The expression vector and expression control sequences are chosen to be compatible with the expression host cell used. The antibody light chain gene and the antibody heavy chain gene can be inserted into separate vectors or, more typically, both genes are inserted into the same expression vector. The antibody genes are inserted into the expression vector by standard methods (*e.g.*, ligation of complementary restriction sites on the antibody gene fragment and vector, or blunt end ligation if no restriction sites are present). Prior to insertion of the antibody-related light or

Please amend page 37, the last paragraph, to read:

A18

As used herein the term "rapamycin compound" includes the neutral tricyclic compound rapamycin, rapamycin derivatives, rapamycin analogs, and other macrolide compounds which are thought to have the same mechanism of action as rapamycin (e.g., inhibition of cytokine function). The language "rapamycin compounds" includes compounds with structural similarity to rapamycin, e.g., compounds with a similar macrocyclic structure, which have been modified to enhance their therapeutic effectiveness. Exemplary rapamycin compounds suitable for use in the invention, as well

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as other methods in which rapamycin has been administered are known in the art (See, e.g. WO 95/22972, WO 95/16691, WO

Please amend page 38, the third paragraph, to read:

The antibodies of the invention are administered to subjects in a biologically compatible form suitable for pharmaceutical administration *in vivo* to inhibit immune responses. By "biologically compatible form suitable for administration *in vivo*" is meant a form of the protein to be administered in which any toxic effects are outweighed by the therapeutic effects of the antibody. The term "subject" is intended to include living organisms in which an immune response can be elicited, e.g., mammals. Examples of subjects include humans, dogs, cats, mice, rats, and transgenic species thereof.

A19

Administration of an antibody of the invention as described herein can be in any pharmacological form including a therapeutically active amount of anti-B7 antibody alone or in combination with an antibody reactive with another B lymphocyte antigen and a pharmaceutically acceptable carrier. Administration of a therapeutically active amount of the therapeutic compositions of the present invention is defined as an amount effective, at dosages and for periods of time necessary to achieve the desired result. For example, a therapeutically active amount of an anti-B7 antibody may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of peptide to elicit a desired response in the individual. A dosage regime may be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

Please amend page 44, the fourth paragraph, to read:

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The contents of all references, pending patent applications and published patents, cited throughout this application are hereby expressly incorporated herein by reference. Each reference disclosed herein is incorporated herein by reference in its entirety. Any

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patent application to which this application claims priority is also incorporated herein by reference in its entirety.

Please amend page 44, the last paragraph, to read:

A21

Intestine grafts were transplanted from B6C3F1/J mice into C57BL/6J wild-type or B7.1$^{-/-}$ B7.2$^{-/-}$ (B7$^{-/-}$) recipients. Wild-type recipients received either no treatment, mCTLA4Ig, or a combination of anti-B7-1 and anti-B7-2 mAbs (for all 3 agents doses were 50 μg every other day at 7 doses). Rejection was graded histologically from 0 to 3 (no to

Please amend page 45, second paragraph, to read:

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Rejection scores of all syngeneic grafts were 0. As indicated by the mean rejection scores shown in Table 1, mCTLA4Ig had no effect on allograft rejection in wild-type mice. In contrast, blockade of the CD28/B7 pathway using anti-B7 mAbs significantly inhibited rejection ($p < 0.05$ at 28 days). The complete disruption of this pathway using B7$^{-/-}$ recipients also resulted in a significant inhibition of rejection ($p < 0.001$). Examination of cytokine gene expression revealed that mCTLA4Ig had little or no effect on IL-2, IFNγ, α-TNF, or IL-12 levels. In contrast, each of these cytokines was significantly decreased in anti-B7 mAb-treated or B7$^{-/-}$ recipients. Similarly, mCTLA4Ig-treated mice expressed levels of the chemokines RANTES and MIP-1 and their receptor CCR5 that were comparable to untreated recipients while anti-B7 mAb-treated and B7-/- recipients expressed decreased levels of these chemokines and CCR5.